

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*

**206911Orig1s000**

**PHARMACOLOGY REVIEW(S)**

**DEPARTMENT OF HEALTH AND HUMAN SERVICES  
PUBLIC HEALTH SERVICE  
FOOD AND DRUG ADMINISTRATION  
CENTER FOR DRUG EVALUATION AND RESEARCH**

**PHARMACOLOGY/TOXICOLOGY NDA REVIEW AND EVALUATION**

Application number: 206911  
Supporting document/s: SDN001  
Applicant's letter date: 6-10-2015  
CDER stamp date: 6-10-2015  
Product: ISV-303 (bromfenac ophthalmic solution 0.075%)  
Indication: Treatment of postoperative inflammation and prevention of ocular pain in patients undergoing cataract surgery  
Applicant: Insite Vision Inc  
965 Atlantic Ave  
Alameda, CA 94501  
Review Division: Division of Transplant and Ophthalmology Products  
Reviewer: Aaron M Ruhland, PhD  
Supervisor/Team Leader: Lori Kotch, PhD, DABT  
Division Director: Renata Albrecht, MD  
Project Manager: Diana Willard

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# 1 Executive Summary

## 1.1 Introduction

The subject of this New Drug Application is BromSite (ISV-303) for the treatment of postoperative inflammation and prevention of ocular pain in patients undergoing cataract surgery. BromSite (bromfenac ophthalmic solution 0.075%), represents a reformulation of previously approved products administered via the same topical ocular route. As 505(b)(2) application, the applicant will rely on the FDA general findings of safety and effectiveness of the listed drug Bromday (bromfenac ophthalmic solution ; 0.09%; NDA 21-664). Also, approved under NDA 21-664 is Xibrom (bromfenac ophthalmic solution ; 0.09%).

The Bromday application (NDA 21-664 SE 2 S-013) presented data to support once daily use of bromfenac ophthalmic solution, 0.09% while the original application for Xibrom indicated twice daily (BID) administration.

Nonclinical data submitted to support approval of ISV-303 include comparative ocular distribution, pharmacokinetic and ocular toxicity assessment. Additionally, the applicant has proposed drug substance impurity specifications for stability which exceed those recommended in ICH guidance. The applicant included nonclinical studies to qualify the impurity specifications. No toxicity was associated with Bromsite which had undergone forced degradation and contained specified impurities at levels which exceed those proposed.

## 1.2 Brief Discussion of Nonclinical Findings

- In a multi-dose study, ISV-303 (0.09% bromfenac) administered 3 times per day (TID) for 14 days yielded bromfenac levels that were highest in the sclera followed by similar levels in the choroid and aqueous humor, and the lowest levels in the vitreous humor.
- Compared to Bromday/Xibrom®, administration of ISV-303 resulted in about 4-fold higher levels in the sclera, choroid and aqueous humor and approximately 1.4-fold higher levels in the vitreous humor.
- Rabbits dosed topically BID with ISV-303 (0.075% or 0.15% bromfenac) or Bromday (0.09% bromfenac) for 29 days showed peak plasma bromfenac concentrations at 0.5 hours with a half-life of approximately 2.8 hours. No accumulation in the plasma was reported. When normalized for the bromfenac dose, the maximum plasma concentrations were similar between ISV-303 (~22 ng/mL) and Bromday/Xibrom (~27 ng/mL).
- The applicant has proposed drug substance impurity specifications for stability which exceed those recommended in ICH guidance. The applicant included nonclinical studies to qualify the impurity specifications. No toxicity was associated with Bromsite which had undergone forced degradation and contained specified impurities at levels which exceed those proposed.

## 1.3 Recommendations

### 1.3.1 Approvability: Approvable

### 1.3.2 Additional Non Clinical Recommendations: None

### 1.3.3 Labeling

#### 1.3.3.1 Applicant's version (Sections relevant to nonclinical Pharmacology/Toxicology)

## 8 USE IN SPECIFIC POPULATIONS

### 8.1 Pregnancy

(b) (4)  
Treatment of rats with bromfenac at oral doses up to 0.9 mg/kg/day (b) (4)  
(b) (4)  
assuming 100% absorbed) and rabbits at oral doses up to 7.5 mg/kg/day  
(b) (4) produced no (b) (4)  
(b) (4) However, embryo-fetal lethality and  
(b) (4) were produced in rats and rabbits at 0.9 mg/kg/day (b) (4)  
(b) (4)

Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

## 12 CLINICAL PHARMACOLOGY

### 12.1 Mechanism of Action

Bromfenac is an NSAID that has anti-inflammatory activity. The mechanism of its action is thought to be due to its ability to block prostaglandin synthesis by inhibiting cyclooxygenase 1 and 2. Prostaglandins have been shown in many animal models to be mediators of certain kinds of intraocular inflammation. In studies performed in animal eyes, prostaglandins have been shown to produce disruption of the blood-aqueous humor barrier, vasodilation, increased vascular permeability, leukocytosis, and increased intraocular pressure.

## 13 NONCLINICAL TOXICOLOGY

### 13.1 Carcinogenesis, Mutagenesis and Impairment of Fertility

Long-term carcinogenicity studies in rats and mice given oral doses of bromfenac up to 0.6 mg/kg/day (b) (4)

(b) (4) assuming 100% absorbed, on a mg (b) (4) basis) and 5 mg/kg/day (b) (4) on a mg (b) (4) basis), respectively revealed no significant increases in tumor incidence.

Bromfenac did not show mutagenic potential in various mutagenicity studies, including the reverse mutation, chromosomal aberration, and micronucleus tests.

Bromfenac did not impair fertility when administered orally to male and female rats at doses up to 0.9 mg/kg/day and 0.3 mg/kg/day, respectively (b) (4), respectively, on a mg/kg basis).

#### 1.3.3.2 Suggested FDA version (Redline; additions appear as double underlined font and deletions appear as ~~strikethrough font~~):

### 8 USE IN SPECIFIC POPULATIONS

#### 8.1 Pregnancy

(b) (4)

Treatment of rats with bromfenac at oral doses up to 0.9 mg/kg/day (b) (4) 195 times (b) (4) a unilateral daily human ophthalmic dose (b) (4) on a mg (b) (4) m<sup>2</sup> basis, assuming 100% absorbed) and rabbits at oral doses up to 7.5 mg/kg/day (b) (4) 3243 times (b) (4) a unilateral daily dose on a mg (b) (4) m<sup>2</sup> basis) produced no (b) (4) structural teratogenicity in reproduction studies. However, embryo-fetal lethality, neonatal mortality and reduced postnatal growth (b) (4) were produced in rats (b) (4) 0.9 mg/kg/day, and embryo-fetal lethality was produced in rabbits at 7.5 mg/kg/day (b) (4).

(b) (4)

-Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

## 12 CLINICAL PHARMACOLOGY

### 12.1 Mechanism of Action

Bromfenac is a <sup>(b) (4)</sup> nonsteroidal anti-inflammatory drug (NSAID) that has anti-inflammatory activity. The mechanism of its action is thought to be due to its ability to block prostaglandin synthesis by inhibiting cyclooxygenase 1 and 2. Prostaglandins have been shown in many animal models to be mediators of certain kinds of intraocular inflammation. In studies performed in animal eyes, prostaglandins have been shown to produce disruption of the blood-aqueous humor barrier, vasodilation, increased vascular permeability, leukocytosis, and increased intraocular pressure.

## 13 NONCLINICAL TOXICOLOGY

### 13.1 Carcinogenesis, Mutagenesis and Impairment of Fertility

Long-term carcinogenicity studies in rats and mice given oral doses of bromfenac up to 0.6 mg/kg/day (<sup>(b) (4)</sup> 129 times <sup>(b) (4)</sup> a unilateral daily dose assuming 100% absorbed, on a mg/<sup>(b) (4)</sup> m<sup>2</sup> basis) and 5 mg/kg/day (<sup>(b) (4)</sup> 540 times <sup>(b) (4)</sup> a unilateral daily dose on a mg/<sup>(b) (4)</sup> m<sup>2</sup> basis), respectively revealed no significant increases in tumor incidence.

Bromfenac did not show mutagenic potential in various mutagenicity studies, including the bacterial reverse mutation, chromosomal aberration, and micronucleus tests.

Bromfenac did not impair fertility when administered orally to male and female rats at doses up to 0.9 mg/kg/day and 0.3 mg/kg/day, respectively (<sup>(b) (4)</sup> 195 and <sup>(b) (4)</sup> 65 times <sup>(b) (4)</sup> a unilateral daily dose, respectively, on a mg/<sup>(b) (4)</sup> m<sup>2</sup> basis).

## 2 Drug Information

### 2.1 Drug

CAS Registry Number: 91714-94-2

Proposed proprietary name: Bromsite

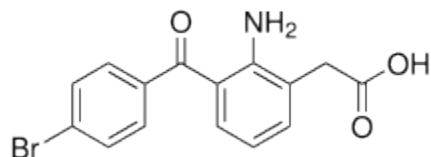
Generic Name: bromfenac ophthalmic solution, 0.075%

Code Name: ISV-303

Chemical Name: 2-[2-amino-3-(4-bromobenzoyl)phenyl]acetic acid

Molecular Formula/Molecular Weight: (b) (4) / (b) (4)

Structure



Pharmacologic Class: Nonsteroidal anti-inflammatory drug (NSAID)

## 2.2 Relevant INDs, NDAs, BLAs and DMFs

- NDA 21664 (Bromday/Xibrom):
  - As 505(b)(2) application, the applicant will rely on the FDA general findings of safety and effectiveness of the listed drug for pharmacology and nonclinical data previously reviewed such as carcinogenicity, genotoxicity, reproductive toxicology, drug interaction, excretion, and metabolism.
  - Approved 3-24-2005 (Xibrom) and 10/2010 (Bromday)
  - A FDA nonclinical review of these data is publicly available.
- NDA 20535: Duract (withdrawn)
  - The systemic formulation has been withdrawn from market due to hepatotoxicity associated with use beyond the recommended duration. NDA 21664 (Bromday) cross-referenced NDA 20535 at the time of application for reliance on nonclinical systemic safety studies.



### 2.3 Drug Formulation

Ingredient	Concentration (%)	Function
Bromfenac sodium sesquihydrate	0.075	Active drug substance
Boric acid	(b) (4)	(b) (4)
Sodium borate		
Citric acid anhydrous		
Sodium citrate dihydrate		
Poloxamer 407		
Benzalkonium chloride		
Polycarbophil	(b) (4)	(b) (4)
Sodium chloride		
Edetate disodium dihydrate		
Sodium hydroxide (b) (4)	to pH8.3	pH adjustment
Water for injection	(b) (4)	

### 2.4 Comments on Novel Excipients

The sponsor refers to the formulation as the DuraSite formulation. Per the sponsor’s website, “DuraSite is a drug delivery vehicle that stabilizes small molecules in a polymeric mucoadhesive matrix. The topical ophthalmic solution can be described as a (b) (4), which extends the residence time of the drug relative to conventional eye drops”/ The Durasite® formulation has been approved for use as a vehicle for other topical ophthalmic products (e.g. Azasite®, NDA 050810). All excipients have been previously qualified for topical ocular administration at or above the concentrations listed in the formulation.

### 2.5 Comments on Impurities/Degradants of Concern

The applicant proposed the following release and stability specifications based on chromatographic purity:

Release:

(b) (4)

Stability

(b) (4)

(b) (4)

The stability specifications exceed those recommended in ICH Q3B. Two studies were conducted to qualify the impurity specifications, Study D-13-303-001 (S11929) and Study D-13-303-009 (S12536). The former study was cancelled early due to two major protocol deviations, animals only being dosed for 29 days instead of the protocol mandated 30 days and, at termination, the left and right eyes were not differentiated (treated versus non-treated). The study was repeated and is reviewed below. No toxicity was associated with Bromsite which had undergone forced degradation and contained impurities (b) (4) at levels which exceed those proposed.

Systemically, a threshold of toxicologic concern (TTC) value of 120 µg/day of a genotoxic impurity administered for less than 1 month is considered to be associated with an acceptable risk (ICH M7: Assessment and control of DNA reactive (mutagenic) impurities in pharmaceuticals to limit potential carcinogenic risk). Following degradation resulting in an impurity concentration of (b) (4)%, the total daily dose of (b) (4) would be (b) (4) µg/day. Since the systemic bioavailability of Bromsite following topical ocular administration is low, the total systemic absorption of the impurity should be considerably less than this amount and should be considered an acceptable potential risk for carcinogenesis. Predictions regarding ocular carcinogenesis cannot be made since a TTC has not been established for ocular tissues.

## 2.6 Proposed Clinical Population and Dosing Regimen

BromSite (bromfenac ophthalmic solution, 0.075%) is indicated for the treatment of postoperative inflammation and prevention of ocular pain in patients undergoing cataract surgery. The recommended dosing is one drop to be applied to the affected eye twice daily (morning and evening) 1 day prior to surgery, the day of surgery, and 14 days post-surgery.

A study determined the mean drop size of Bromsite to be (b) (4) mL (D-13-303-004.00R). The total daily dose of bromfenac is (b) (4) or (b) (4) if administered bilaterally.

## 3 Studies Submitted

### 3.1 Studies Reviewed

#### Pharmacokinetics

- Report 08-4624-N1: Ocular distribution study of bromfenac formulation following repeated topical ocular administration
- Report 08-4624-N2: Ocular pharmacokinetic study of bromfenac formulation following topical ocular administration

## Toxicology

- Report S10251: 14-day ocular toxicity of ISV-303 eye drop formulations in Dutch Belted rabbits
- Report S11135: 29-day ocular toxicity of ISV-303 eye drop formulations in Dutch Belted rabbits
- Report D-13-303-009 (S12536): A 30-day toxicology study followed by an undetermined recovery period to evaluate the safety of ISV-303 bromfenac degradation products in Dutch Belted rabbits
- Report MB 13-21639.30: 3T3 Neutral Red uptake assay

## 3.2 Studies Not Reviewed

### Pharmacokinetics

- Report ARBROM6: Method validation report for the determination of bromfenac in human and rabbit aqueous humor using LC-API/MS/MS
- Report ARBROM7: Method validation report for the determination of bromfenac in rabbit plasma (K<sub>2</sub>EDTA) using LC-API/MS/MS
- Report S11136: Comparison of ISV-303 eye drop formulations in Dutch Belted rabbits
- Report: Scintigraphic evaluation of 99mTc labeled ophthalmic formulations in the rabbit model – A pilot study

### Toxicology

- Report D-13-303-001 (S11929): A 30-day toxicology study followed by an undetermined recovery period to evaluate the safety of ISV-303 bromfenac degradation products in Dutch Belted rabbits
  - Major protocol deviations; study repeated
- Report 2584-100: Chronic ocular toxicity study in rabbits
  - (Reviewer's note: Toxicity study of the Durasite® vehicle)

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### 3.3 Previous Reviews Referenced

- NDA 21-664 SDN001
  - Pharmacology/Toxicology Review
    - Author: Conrad Chen, PhD
    - Dated: 2-4-2005

## 4 Pharmacology

### 4.1 Primary Pharmacology

Excerpted from Dr. Chen’s NDA 21-664 Review (2005):

*Bromfenac sodium, AHR-10282b, is a cyclooxygenase inhibitor possessing analgesic, anti-inflammatory, and antipyretic activities in various animal experimental models. It belongs to a non-steroidal anti-inflammatory drug class (NSAID) without any narcotic-like activity. Bromfenac did not possess any significant effects on the central nervous system and cardiovascular function.*

*Bromfenac sodium inhibited both arachidonic acid and carrageenan-induced conjunctival edema in a dose-dependent manner, and the increase of aqueous humor protein typically seen in response to paracentesis and laser energy application. Bromfenac sodium demonstrated greater inhibition of acute chemosis in comparison with pranoprofen ophthalmic solution (PPF), an ophthalmic solution marketed in Japan. Further, the inhibition of increased aqueous humor protein induced by paracentesis was 8 to 10 times greater than that seen with PPF. Bromfenac sodium ophthalmic solution instilled QID demonstrated significant inhibition in the experimental uveitis rabbit model (a chronic ocular inflammation model), and its effect was maintained when the frequency of instillation was reduced to BID. In the same model, PPF demonstrated significant inhibition when instilled QID but not BID.*

*In a series of animal studies, bromfenac sodium was effective in inhibiting both cyclooxygenase 1 and 2, thereby inhibiting the inflammatory reactions induced by mediators such as prostaglandins.*

### **4.3 Safety Pharmacology**

Excerpted from NDA 21-664 Review (2005):

*Studies in cats (from the NDA 20-535 review) revealed that bromfenac sodium did not have effects on central nervous system (behavior and normal spontaneous cerebral activities). Results obtained from the studies in dogs indicated that bromfenac sodium did not have anti-adrenergic and anti-histaminic properties, but it had little or limited effects on cardiovascular function. As to the respiratory and circulatory organs, a transient increase in the systolic, mean and diastolic blood pressure, as well as an increase in femoral artery blood flow, was observed after intravenous administration at 10 mg/kg. This change was considered to be a common feature of drugs of this class. With respect to the water and electrolyte metabolism, oral administration of bromfenac sodium at 1 or 3 mg/kg decreased urine volume and urinary electrolyte excretion volumes (Na<sup>+</sup>, K<sup>+</sup>, Cl<sup>-</sup>). At a dosage of 10 or 100 mg/kg, decreased urine volume and urinary Na<sup>+</sup> and Cl<sup>-</sup> excretion volume were observed. However, it was reported that the urine volume was decreased in rats due to acute inhibition of Na<sup>+</sup> excretion after administration of various NSAIDs. Accordingly, these changes are considered as common features of NSAIDs. The investigation of the safety pharmacology of bromfenac sodium did not indicate any action that caused a clinical concern.*

## 5 Pharmacokinetics/ADME/Toxicokinetics

### 5.1 General PK/ADME

Excerpted from NDA 21-664 Review (2005):

*Bromfenac sodium is absorbed well after oral dosing and is distributed to most tissues after oral or intravenous dosing. Bromfenac is not extensively metabolized, with the parent compound representing the majority of the drug-related material in plasma, whether the drug is administered orally, intravenously, or by topical instillation. The compound is cleared rapidly from all tissues with greater than 90% of the dose being recovered in excreta by 48 hours post dosing. Bromfenac sodium is excreted in both urine and feces, with some enterohepatic recirculation occurring in rats. The compound binds significantly to plasma proteins, but does not have a high affinity to bind to melanin.*

### 5.2 Ocular Pharmacokinetics

#### Report 08-4624-N1: Ocular distribution study of bromfenac formulation following repeated topical ocular administration

Conducting laboratory and location:



Date of study initiation: 12/5/2008  
GLP compliance: No  
QA statement: Yes  
Drug, lot #, and % purity: ISV-303, Lot IVE-4190

#### Methods

Doses: Right eye: Xibrom (bromfenac 0.09%)  
Left eye: ISV-303 (bromfenac 0.09%)  
Frequency of dosing: Three times daily for 14 days  
Route of administration: Topical ocular  
Dose volume: 0.04 mL  
Species/Strain: Rabbit / Dutch Belted  
Number/Sex/Group: 3/sex  
Age: > 10 weeks  
Weight: 1.56 – 1.82 kg

This study compared the ocular distribution of bromfenac in Dutch-Belted rabbits two hours following topical application of Xibrom™ or 0.09% ISV-303. Xibrom was

administered to the right eye while ISV-303 was administered to the left eye, three times daily for 14 consecutive days. Throughout the dosing period, eyes were examined and scored according to the McDonald–Shadduck Scoring System for Ocular Lesions and clinical signs of toxicity. Eyes were collected 2 hours following the last dose to assay for bromfenac content.

**Reviewer’s note:** The study design does not take into consideration any systemic exposure following topical application of bromfenac to either eye affecting intraocular concentrations of bromfenac measured in the contralateral eye. Bromfenac is known to disrupt the blood-aqueous humor barrier and thus this possibility should be considered.

There were no signs of toxicity that were considered adverse and related to treatment. When values were pooled across sexes the concentration of bromfenac in the sclera, choroid, vitreous and aqueous humor from the left eye after treatment with 0.09% ISV-303 were significantly higher than concentrations in these tissues from the right eye after treatment with Xibrom™. The ISV-303 formulation increased intraocular concentrations of bromfenac up to 4-fold.

Tissue	0.09% ISV-303*	Xibrom	Fold Difference	p value
Sclera	3877	1103	+3.51-fold	p < 0.01
Choroid	255	78.1	+3.26-fold	p < 0.0001
Retina	34.3	32.4	+1.05-fold	Not significant
Vitreous humor	1.8	1.3	+1.4-fold	p < 0.05
Aqueous humor	221.3	55.9	+3.95-fold	p < 0.01

\*Note that the concentration proposed for marketing is 0.075%

### Report 08-4624-N2: Ocular pharmacokinetic study of bromfenac formulation following topical ocular administration

Conducting laboratory and location:



Date of study initiation: 10/30/2008  
 GLP compliance: No  
 QA statement: Yes  
 Drug, lot #, and % purity: ISV-303 (0.09% bromfenac): Lot IVE-4190  
 ISV-303 (0.045% bromfenac): Lot IVE-4193  
 Xibrom: Lot 297241



## Methods

Doses: Right eye: Xibrom (bromfenac 0.09%)  
Left eye: DuraSite formulation (bromfenac 0.09%)  
Frequency of dosing: Single dose  
Route of administration: Topical ocular  
Dose volume: 0.04 mL  
Species/Strain: Rabbit / Dutch Belted  
Number/Sex/Group: 3/sex/treatment/time point (sacrificed)  
Age:  $\geq 10$  weeks  
Weight: 1.20 – 1.93 kg

The pharmacokinetics of 0.045 % and 0.09% ISV-303 were compared to Xibrom™ following topical ocular administration in Dutch-Belted rabbits. Throughout the dosing period, eyes were examined and scored according to the McDonald–Shaddock Scoring System for Ocular Lesions and clinical signs of toxicity.

No treatment related signs of systemic toxicity or ocular irritation were evident during the study. The concentration of bromfenac in the aqueous humor was determined at 0.5, 1, 2, 4, 8, 12, and 24 hours post-dose. Treatment with 0.045% and 0.09% ISV-303 resulted in significantly higher concentrations of bromfenac in the aqueous humor at 1, 4, 8, and 12 hours post dose than treatment with Xibrom. The concentration was also significantly higher at 0.5 hours after treatment with 0.045% ISV-303 than Xibrom. The pharmacokinetic profiles of ISV-303 in aqueous humor differed from that of Xibrom. While  $t_{1/2}$  was comparable across all treatments, the  $T_{max}$  was shorter after treatment with 0.045% and 0.09% ISV-303 than the corresponding  $T_{max}$  values of Xibrom.  $C_{max}$ ,  $T_{max}$ ,  $AUC_t$ , and  $AUC_i$  increased with a dose increase from 0.045% and 0.09% ISV-303 formulations.  $C_{max}$ ,  $AUC_t$ , and  $AUC_i$  were greater for both the 0.045% and 0.09% ISV-303 formulations relative to the corresponding values of these parameters for Xibrom. This indicates that the overall exposure of bromfenac in the aqueous humor was greater after a single treatment with 0.045% and 0.09% ISV-303 than after a single treatment with Xibrom. Following a single administration of 0.045 % or 0.09% ISV-303 or Xibrom™, bromfenac concentrations dropped appreciably by 8 hours, but were detectable in the in aqueous humor up to 24 hours.

### **Concentration in the aqueous humor following topical ocular administration**

Time point (hrs)	ISV-303 (0.045%)	Xibrom (0.09%)	Fold Difference (increase over Xibrom)	p value
0.5	151.2	36.2	+4.2-fold	p < 0.05
1	70.6	30.6	+2.3-fold	p < 0.05
2	59.3	40.1	+1.5-fold	p < 0.05
4	69.1	25.7	+2.7-fold	p < 0.01
8	20.2	8.1	+2.5-fold	p < 0.05
12	6.2	4.0	+1.6-fold	p < 0.05
24	0.651	0.588	+1.1-fold	NA

### Concentration in the aqueous humor following topical ocular administration

Time point (hrs)	ISV-303 (0.09%)	Xibrom (0.09%)	Fold Difference (increase over Xibrom)	p value
0.5	175.9	32.6	5.4-fold	p < 0.05
1	317.8	38.7	8.2-fold	p < 0.01
2	125.3	95.3	1.3-fold	p > 0.05
4	139.6	31.6	4.4-fold	p < 0.01
8	37.6	8.2	4.6-fold	p < 0.01
12	17.2	3.7	4.6-fold	p < 0.05
24	1.081	BLQ	NA	NA

Parameter	ISV-303 (0.045%)	Xibrom (0.09%)	ISV-303 (0.09%)	Xibrom (0.09%)
C <sub>max</sub> (ng/g)	151	40	318	95.3
T <sub>max</sub> (h)	0.5	2	1	2
K (h <sup>-1</sup> )	0.3	0.3	0.2	0.3
T <sub>1/2</sub>	2.9	2.6	2.9	2.2
AUC <sub>t</sub> (ng·h/g)	557	243	1230	345
AUC <sub>∞</sub> (ng·h/g)	559	244	1230	345

## 6 General Toxicology

### 6.1 Single-Dose Toxicity

Proprietary data analysis excerpted from Chen's NDA 21-664 Review (2005):

*In the acute toxicity study, the LD50 for female rats was 39.6 mg/kg po and 15.0 mg/kg iv, and for male rats was 46.0 mg/kg iv. The predominant toxicity observed*

*in these studies was GI related. Hemorrhagic spots in the GI tract, thickened intestinal walls, and adhesions of intestine to peritoneal walls were major characteristics of GI lesions. Kidney toxicity was also observed, which included hematuria and pale kidneys at necropsy. The maximum nontoxic doses were  $\leq 10$  mg/kg po for the rat, rabbit and dog, and  $\leq 1.0$  mg/kg iv for the rat. It appeared that female rats were more susceptible to Bromfenac-caused toxicity than male rats.*

## **6.2 Repeat-Dose Toxicity**


### **General Systemic Toxicology:**

Proprietary data analysis excerpted from Chen's NDA 21-664 Review(2005):

*In a 13-week toxicity study in rats, no treatment-related toxicities were found in animals at  $\leq 0.5$  mg/kg/day. At 2.5 mg/kg/day, intestinal ulcers/necrosis was observed. In a 24-month study in rats, dose-dependent hepatic (vacuolar alterations, cytoplasmic changes, inflammation, and necrosis) and gastrointestinal (inflammation, and necrosis) toxicities were identified at 12- and 24-month postmortem macro- and/or micro-scopic examinations. Nephrotoxicity (papillary necrosis) was also revealed at terminal necropsy. However, there were no treatment-associated increased in the tumor incidences in animals. No drug-related macro- and microscopic changes were observed during the six-month interim sacrifices in all doses (0.05, 0.3, and 0.6 mg/kg/day). It appeared that female rats were more sensitive to intestinal toxicity than male rats in this study. In a 13-week study in rhesus monkeys, no toxicity was found at 15 mg/kg/day. Emesis was found at 45 and 135 mg/kg/day and GI lesions were found at 135 mg/kg/day. A 12-month study was conducted in cynomolgus monkeys. Treatment-related death and enteric toxicity (ulcers) occurred in animals receiving 10 and 30 mg/kg/day in this study.*

### **Ocular Toxicology:**

**Study title: 14-day ocular toxicity of ISV-303 eye drop formulations in Dutch Belted rabbits**

Study no.: S10251  
Study report location: SDN001: 4.2.3.2  
Conducting laboratory and location:  (b) (4)  
Date of study initiation: 12-21-2009  
GLP compliance: Yes  
QA statement: Yes  
Drug, lot #, and % purity: ISV-303 (0.045%), IVE-4225, >99%  
ISV-303 (0.09%), IVE 4226, >99%  
ISV-303 (0.18%), IVE 4227, >99%

**Key Study Findings**

- Topical ocular instillation of ISV-303 (0.045% - 0.18%) to Dutch-Belted rabbits twice daily for 14 days elicited no evidence of ocular irritation or systemic toxicity and no dose related effects on specific ocular indices (tonometry, macroscopic examination, slit lamp biomicroscopy, ophthalmoscope examination, and ocular histopathology).
- The NOAEL considered to be the high dose, ~126 µg/eye/day.

**Methods**

Doses: 0.045%, 0.09%, 0.18%  
Frequency of dosing: BID for 14-days  
Route of administration: Left eye only; topical ocular administration  
Dose volume: 0.035 mL  
Formulation/Vehicle: DuraSite  
Species/Strain: Rabbit / Dutch Belted  
Number/Sex/Group: 3/sex/group  
Age: 5 months  
Weight: 1.969 – 2.181 kg  
Deviation from study protocol: None which affected results or interpretability

**Observations and Results****Mortality (twice daily)**

- No animals died or were euthanized prior to the scheduled sacrifice

**Clinical Signs (prior to dosing phase, weekly)**

- No changes in clinical signs were attributed to the test article

**Body Weights (prior to dosing phase, Days 1, 7, 14)**

- No changes in body weight gain or loss were attributed to the test article.

**Food Consumption (prior to dosing phase, weekly)**

- No changes in food consumption were attributed to the test article.

**Ophthalmoscopy (slit-lamp / indirect funduscopy / tonometry; prior to dosing phase, Day 14)**

- Ocular discharge in the left eye
  - All groups including vehicle control
  - Mild (grade 1)
  - Usually noted as a white material in medial canthus of the eye
  - More common following the last dose of the day.
  - Not considered to be related to the test article
- No other changes in ophthalmoscopic observations or intraocular pressure were attributed to the test article

**Hematology (prior to dosing phase, Day 14)**

**No changes in hematological parameters were attributed to the test article**

**Clinical Chemistry (prior to dosing phase, Day 14)**

- No changes in clinical chemistry parameters were attributed to the test article

**Urinalysis (prior to dosing phase, Day 14)**

- No changes in urinalysis parameters were attributed to the test article

**Gross Pathology**

- No macroscopic changes at necropsy were attributed to the test article

**Organ Weights**

- No changes in organ weights were attributed to the test article

**Histopathology**

Adequate Battery: Ocular tissues only (adequate)

Peer Review: No

Histological Findings:

- Lymphoplasmacytic infiltrate
  - Mild
  - Primarily located at limbus or palpebral conjunctiva

- Noted in treated eyes from animals in all groups including vehicle control


**Toxicokinetics (Day 1: predose, and 30 minutes, 1, 2, 4 and 8 hours post-dose and Day 29: predose, and 30 minutes, 1, 2, 4, 8, 12 and 24 hours post-dose)**

- Not performed

**Dosing Solution Analysis**

- All dosing solutions were found within specifications at the post-study analysis

**Study title: 29-day ocular toxicity of ISV-303 eye drop formulations in Dutch Belted rabbits**

Study no.:	S11135
Study report location:	SDN001: 4.2.3.2
Conducting laboratory and location:	 (b) (4)
Date of study initiation:	10-17-2011
GLP compliance:	Yes
QA statement:	Yes
Drug, lot #, and % purity:	ISV-303 (0.075%), IVE-4285, 90 - 100% ISV-303 (0.15%), IVE 4286, 90 - 100% Xibrom (0.09%)

**Key Study Findings**

- Topical ocular administration of ISV-303 (bromfenac 0.075% or 0.15%) or its vehicle was associated with increased incidence of a mild discharge in the eye receiving the dose
- No other ocular or systemic toxicity was associated with twice daily administration of ISV-303 for 29 days
- The high dose, 0.15% BID, represents a 2-fold increase over the proposed clinical regimen

**Methods**

Doses: Group 2: ISV-303 0.075%  
Group 3: ISV-303 0.15%  
Group 4: Xibrom: 0.09%

Frequency of dosing: BID for 29-days  
Route of administration: Left eye only; topical ocular administration  
Dose volume: 0.035 mL  
Formulation/Vehicle: DuraSite vehicle (Note: not applicable as control for Xibrom)  
Species/Strain: Rabbit / Dutch Belted  
Number/Sex/Group: 4/sex/group  
Age: ~6 months  
Weight: 1.475 – 2.083 kg  
Deviation from study protocol: None which affected results or interpretability

**Observations and Results****Mortality (twice daily)**

- No animals died or were euthanized prior to the scheduled sacrifice

**Clinical Signs (prior to dosing phase, weekly)**

- No changes in clinical signs were attributed to the test article

**Body Weights (prior to dosing phase, weekly, prior to necropsy)**

- No changes in body weight gain or loss were attributed to the test article.

**Food Consumption (prior to dosing phase, weekly)**

- No changes in food consumption were attributed to the test article.

**Ophthalmoscopy (slit-lamp / indirect funduscopy / tonometry; prior to dosing phase, Day 28)**

- No changes in ophthalmoscopic observations or intraocular pressure were attributed to the test article

**Hematology (prior to dosing phase, Day 25)**

- No changes in hematological parameters were attributed to the test article

**Clinical Chemistry (prior to dosing phase, Day 25)**

- No changes in clinical chemistry parameters were attributed to the test article

**Urinalysis (prior to dosing phase, Day 28)**

- No changes in urinalysis parameters were attributed to the test article

### Gross Pathology

- No macroscopic changes at necropsy were attributed to the test article

### Organ Weights

- No changes in organ weights were attributed to the test article

### Histopathology

Adequate Battery: Ocular tissues only (adequate)

Peer Review: No

Histological Findings:

- Lymphoplasmacytic infiltrate
  - Mild
  - Primarily located at limbus or palpebral conjunctiva
  - Noted in treated eyes from animals in both eyes of all groups including Xibrom and vehicle control. Considered common and secondary to environmental irritation

### Dosing Solution Analysis

- All dosing solutions were found within specifications at the post-study analysis

### Toxicokinetics

Dose group	ISV-303 (0.075%)		ISV-303 (0.15%)		Xibrom (0.09%)	
	1	29	1	29	1	29
Day						
$C_{max}$ (ng/mL)	18.5	21.7	54.6	51.2	21	26.7
$T_{max}$ (h)	0.5	0.5	0.5	0.5	0.5	0.5
$t_{1/2}$ (h)	2.83	2.85	2.20	2.50	2.46	2.46
$AUC_{0-8}$ (ng·hr/mL)	34.3	37.1	90.4	83.0	34.0	40.5
$AUC_{last}$ (ng·hr/mL)	34.3	42.4	90.4	94.7	34.0	44.6



**Study title: A 30-day toxicology study followed by an undetermined recovery period to evaluate the safety of ISV-303 bromfenac degradation products in Dutch Belted rabbits**

Study no.: D-13-303-009 (S12536)  
 Study report location: SDN001: 4.2.3.7.6  
 Conducting laboratory and location: (b) (4)  
 Date of study initiation: 9/24/2013  
 GLP compliance: Yes  
 QA statement: Yes  
 Drug, lot #, and % purity: ISV-303, Lot 0313G, 99.9%

**Key Study Findings**

- Degraded ISV-303 containing (b) (4) was not associated with increased ocular or systemic toxicity following topical ocular administration
- The study results qualify the applicant's stability specifications for the drug product of NMT (b) (4)% and NMT (b) (4)% for (b) (4), respectively.

**Methods**

Doses: ISV-303 (bromfenac 0.075%)  
 Degraded ISV-303 (bromfenac: 0.075%, (b) (4))  
 Frequency of dosing: Three times daily for 30-days (right eye only)  
 Route of administration: Topical ocular drop  
 Dose volume: 0.04 mL/drop  
 Formulation/Vehicle: Durasite vehicle  
 Species/Strain: Rabbit / Dutch Belted  
 Number/Sex/Group: 6/sex/group  
 Age: 4 months  
 Weight: 1.3 – 1.6 kg  
 Deviation from study protocol: As there were no observed clinical pathology or ophthalmic toxicities prior to the termination of dosing phase, it was deemed unnecessary to have a recovery period of up to 28 days. All animals were sacrificed on Day 31. No other deviations affected results or interpretation

**Observations and Results**

**Mortality (twice daily)**

- No animals died or were euthanized prior to scheduled sacrifice on Day 31

**Clinical Signs (pre-dosing period; weekly)**

- No changes in clinical signs were attributed to the test article

**Body Weights (pre-dosing period; weekly, prior to necropsy)**

- No changes in body weights were attributed to the test article

**Feed Consumption (weekly)**

- No changes in food consumption were attributed to the test article

**Ophthalmoscopy (pre-dosing period and Day 30)**

- No changes in ophthalmoscopic observations were attributed to the test article

**Tonometry (pre-dosing period and Day 30)**

- No changes in intraocular pressure were attributed to the test article

**Hematology (pre-dosing period and Day 30)**

- No changes in hematological parameters were attributed to the test article

**Clinical Chemistry (pre-dosing period and Day 30)**

- No changes in clinical chemistry parameters were attributed to the test article

**Urinalysis (pre-dosing period and Day 30)**

- No changes in urinalysis were attributed to the test article

**Gross Pathology (Day 31)**

- No changes in gross macroscopic observations were attributed to the test article

**Organ Weights**

- No changes in organ weights were attributed to the test article

**Histopathology**

Battery: Ocular tissues only

Peer Review: No

**Histological Findings**

- No changes in microscopic observations were attributed to the test article

## 7 Genetic Toxicology

As a 505(b)(2) application, the applicant will rely on the Agency's previous findings for Bromday® (NDA 21664) regarding genotoxicity. The following information is contained within the labeling for Bromday®:

*Bromfenac did not show mutagenic potential in various mutagenicity studies, including the reverse mutation, chromosomal aberration, and micronucleus tests.*

This statement can be applied in the labeling for the current application, with the addition of the word '*bacterial*' before reverse mutation to adequately describe the assay.

## 8 Carcinogenicity

As a 505(b)(2) application, the applicant will rely on the Agency's previous findings for Bromday® (NDA 21664) regarding carcinogenicity. The following information is contained within the labeling for Bromday®:



This statement from the Bromday labeling contains sufficient information to allow safety margins for Bromsite to be calculated. The maximum RHOD reported in the Bromday labeling is based upon bilateral dose administration and the safety margins are based on a direct comparison of dose and body mass (mg/kg) whereas the safety margins should be based on dose and body surface area comparison (mg/m<sup>2</sup>). For Bromsite, the labeling regarding carcinogenicity should state:

Long-term carcinogenicity studies in rats and mice given oral doses of bromfenac up to 0.6 mg/kg/day (65-times the maximum recommended human ophthalmic dose [RHOD] on a mg/m<sup>2</sup> basis, assuming 100% absorbed) and 5 mg/kg/day (270- times the maximum RHOD), respectively, revealed no significant increases in tumor incidence.

## 9 Reproductive and Developmental Toxicology

As a 505(b)(2) application, the applicant will rely on the Agency's previous findings for Bromday® (NDA 21664) regarding reproductive and developmental toxicology. The following information is contained within the labeling for Bromday®:

This statement from the Bromday labeling contains sufficient information to allow safety margins for Bromsite to be calculated. For Bromsite, the labeling regarding reproductive and developmental toxicity should state:

### 8.1 Pregnancy

There are no adequate and well-controlled studies in pregnant women. Treatment of pregnant rats and rabbits with oral bromfenac did not produce teratogenic effects at clinically relevant doses.

Treatment of rats with bromfenac at oral doses up to 0.9 mg/kg/day ( (b) (4) 195 times a unilateral daily human ophthalmic dose on a mg/m<sup>2</sup> basis, assuming 100% absorbed) and rabbits at oral doses up to 7.5 mg/kg/day (3243 times a unilateral daily dose on a mg/m<sup>2</sup> basis) produced no structural teratogenicity in reproduction studies. However, embryo-fetal lethality, neonatal mortality and reduced postnatal growth were produced in rats at 0.9 mg/kg/day, and embryo-fetal lethality was produced in rabbits at 7.5 mg/kg/day.

Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

#### *Clinical considerations*

Because of the known effects of prostaglandin biosynthesis-inhibiting drugs on the fetal cardiovascular system (closure of ductus arteriosus), the use of BromSite during late pregnancy should be avoided.

## 10 Special Toxicology Studies

### Report MB 13-21639.30: 3T3 Neutral Red uptake assay

Balb/c 3T3 mouse fibroblast cell line was pre-incubated with various concentrations of bromfenac (68.1 – 1000 µg/mL) for 1 hour prior to exposure to solar simulated light (SSL; 5 J/cm<sup>2</sup>) or dark. Following 50-minute exposure, the treatment medium was placed with culture medium and, after 24 hours, cell viability was determined by neutral red uptake assay.

The Photo-Irritant-Factor (PIF) model compares the effect of a compound in the presence (+SSL) and absence (No SSL) of SSL irradiation at a single concentration - that concentration at which cytotoxicity occurs for 50% of the cells. According to this model, a compound was considered to have phototoxic potential if  $PIF = EC_{50 \text{ NoSSL}} / EC_{50 \text{ +SSL}} > 5.0$ . The PIF model predicts "probable phototoxicity" if the PIF  $> 2.0$  and  $< 5.0$ .

The Mean Photo Effect (MPE) model was based on comparison of the complete concentration response curves. According to the MPE model, a test substance was considered to have phototoxic potential if the MPE  $> 0.15$ . Also, a test substance was considered to exhibit "probable phototoxicity" if the MPE  $> 0.1$  and  $< 0.15$ .

PIF model results indicated that bromfenac has probable phototoxicity, while the MPE model predicts bromfenac as having phototoxic potential.

Test article	Concentration range tested	EC50 No SSL	EC50 +SSL	PIF	MPE
Bromfenac sodium, Lot/Batch# IVR-1330	68.1 – 1000 µg/mL	> 1000 µg/mL	348.3 µg/mL	> 2.9	0.384
Chlorpromazine (positive control)	No SSL: 6.81 – 100 µg/mL +SSL: 0.22 – 3.16 µg/mL	21.8 µg/mL	0.7 µg/mL	31.1	0.491

Given limited systemic exposure following ocular administration, distribution to skin would likely be minimal, thus limiting systemic concern. The relevance of 3T3 Neutral Red uptake assay, which uses fibroblast cell lines, to ocular tissues is unknown.

## 11 Integrated Summary and Safety Evaluation

The applicant has proposed BromSite (ISV-303) for the treatment of postoperative inflammation and prevention of ocular pain in patients undergoing cataract surgery. BromSite (bromfenac ophthalmic solution 0.075%), represents a reformulation of previously approved products administered via the same topical ocular route.

Nonclinical data submitted to support approval of ISV-303 include comparative ocular distribution, pharmacokinetic and ocular toxicity assessment. Compared to BromDay/Xibrom®, administration of ISV-303 resulted in approximately 4-fold higher levels in the sclera, choroid and aqueous humor and approximately 1.4-fold higher levels in the vitreous humor. The increased exposure was not associated with ocular toxicity when rabbits were dosed topically BID with up to 0.18% ISV-303 for 14 days.

The applicant proposed drug substance impurity specifications for stability which exceed those recommended in ICH guidance. The applicant included nonclinical studies to qualify the impurity specifications. No toxicity was associated with Bromsite which had undergone forced degradation and contained specified impurities levels which exceed those proposed.

Toxicity	Species	NOAEL	Safety Margin Based on ocular dose*
No adverse ocular toxicity	Rabbit	0.18% BID (126 µg/eye/day)	2.8-fold

\*human unilateral ocular dose is one drop, twice daily (45 µg/eye/day)

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/s/  
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AARON M RUHLAND  
03/15/2016

LORI E KOTCH  
03/15/2016

# PHARMACOLOGY/TOXICOLOGY FILING CHECKLIST FOR NDA

**NDA Number: 206911**

**Applicant: InSite Vision**

**Stamp Date: 6-10-2015**

**Drug Name: ISV-303**

**NDA/BLA Type: 505(b)(2)**

**Original NDA (SD1)**

On **initial** overview of the NDA/BLA application for filing:

	Content Parameter	Yes	No	Comment
1	Is the pharmacology/toxicology section organized in accord with current regulations and guidelines for format and content in a manner to allow substantive review to begin?	✓		
2	Is the pharmacology/toxicology section indexed and paginated in a manner allowing substantive review to begin?	✓		
3	Is the pharmacology/toxicology section legible so that substantive review can begin?	✓		
4	Are all required (*) and requested IND studies (in accord with 505 b1 and b2 including referenced literature) completed and submitted (carcinogenicity, mutagenicity, teratogenicity, effects on fertility, juvenile studies, acute and repeat dose adult animal studies, animal ADME studies, safety pharmacology, etc)?	✓		*As 505(b)(2), applicant relies on Xibrom/Bromday (NDA 21-664) for primary pharmacology, safety pharmacology, pharmacokinetics, genotoxicity, reproductive and developmental toxicology, carcinogenicity and systemic toxicology. Applicant has conducted repeat dose ocular toxicity (28-day), and comparative ocular distribution and systemic absorption studies of the ISV-303 formulation.
5	If the formulation to be marketed is different from the formulation used in the toxicology studies, have studies by the appropriate route been conducted with appropriate formulations? (For other than the oral route, some studies may be by routes different from the clinical route intentionally and by desire of the FDA).	✓		
6	Does the route of administration used in the animal studies appear to be the same as the intended human exposure route? If not, has the applicant <u>submitted</u> a rationale to justify the alternative route?	✓		

File name: 5\_Pharmacology\_Toxicology Filing Checklist for NDA\_BLA or Supplement 010908



## PHARMACOLOGY/TOXICOLOGY FILING CHECKLIST FOR NDA

	Content Parameter	Yes	No	Comment
7	Has the applicant <u>submitted</u> a statement(s) that all of the pivotal pharm/tox studies have been performed in accordance with the GLP regulations (21 CFR 58) <u>or</u> an explanation for any significant deviations?	✓		*Study D-13-303-001: 30-day toxicity study of degraded ISV-303 in rabbits was non-GLP and terminated early due to major protocol deviations by CRO
8	Has the applicant submitted all special studies/data requested by the Division during pre-submission discussions?	✓		* Systemic PK bridging study and phototoxicity analysis requested in Division letter dated 1-7-2014 included.
9	Are the proposed labeling sections relative to pharmacology/toxicology appropriate (including human dose multiples expressed in either mg/m <sup>2</sup> or comparative serum/plasma levels) and in accordance with 201.57?		✓	Like the approved Bromday labeling, the safety margins are calculated based on direct dose comparison (mg/kg). A decision to convert safety margins based on body surface area comparison (mg/m <sup>2</sup> ) will be made during review.
10	Have any impurity – etc. issues been addressed? (New toxicity studies may not be needed.)	✓		No issues have been apparent thus far. Pharm/Tox will await confirmation from the CMC discipline.
11	Has the applicant addressed any abuse potential issues in the submission?			-Not applicable
12	If this NDA/BLA is to support a Rx to OTC switch, have all relevant studies been submitted?			-Not applicable

**IS THE PHARMACOLOGY/TOXICOLOGY SECTION OF THE APPLICATION FILEABLE? Yes.**

Please identify and list any potential review issues to be forwarded to the Applicant for the 74-day letter.

None.

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Reviewing Pharmacologist

Date

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Team Leader/Supervisor

Date

File name: 5\_Pharmacology\_Toxicology Filing Checklist for NDA\_BLA or Supplement 010908

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**This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.**  
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/s/  
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AARON M RUHLAND  
07/27/2015

LORI E KOTCH  
07/27/2015